REGN475

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REGN475 Overview

- Fully human monoclonal antibody (IgG4)
- Specifically binds to human, monkey, mouse, and rat NGF
- Blocks NGF signaling through both TrkA and p75 receptors
- Does not bind to or block cell signaling of other neurotrophins (NT-3, NT-4 / 5, or BDNF)

Agenda

- **Introduction**
- **Phase 2 Efficacy and Safety**
- **Joint-Related Safety**
- **Preliminary Nonclinical Data**
- **Regeneron and Sanofi Conclusions**
- **Sponsors' Proposed Path Forward**

Regeneron / Sanofi Position

Assessment of current data:

- **Evidence for efficacy**
- **Possible role for anti-NGF therapy in pain conditions where there is unmet need**
- **Concerning safety signals**
- **Not for all patients with OA or other pain**
  - **Until safety is better understood**

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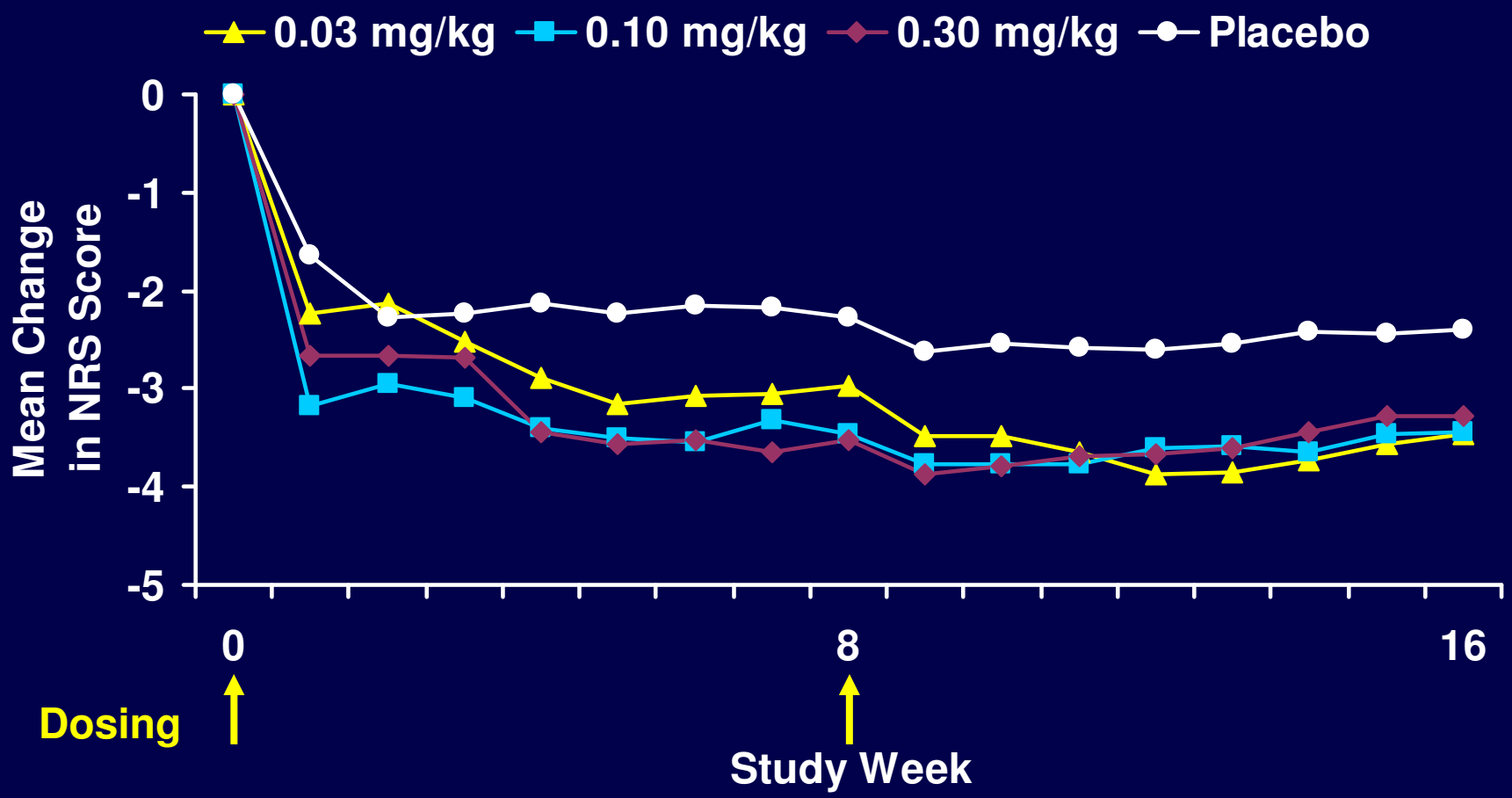
REGN475 Clinical Program

- **The clinical program to-date:**
  - Ascending, Single-Dose FIH study in NHV (n = 56)
  - OA of the Knee (n = 215)
  - Sciatic Pain (n = 158)
  - Thermal Injury Pain (n = 0)
  - Chronic Pancreatitis Pain (n = 15)
  - Vertebral Fracture Pain associated with Osteoporosis (n = 40)
  - Safety and PK Study (new formulation) (n = 25)
  - **Total number of subjects / patients: 509**
  - **Total number exposed to active drug: 357**

REGN475 Improved NRS Walking Knee Pain in Patients with OA



Musculoskeletal And Nervous System AEs (>2% with REGN475) Reported in the R475-PN-0901 OA Study

	Placebo (n=55) n (%)	REGN475 0.03 (n=56) n (%)	REGN475 0.1 (n=52) n (%)	REGN475 0.3 (n=52) n (%)
Musculoskeletal System	**14 (25.5%)**	**10 (17.9%)**	**14 (26.9%)**	**19 (36.5%)**
Arthralgia	3 (6%)	2 (4%)	10 (19%)	8 (15%)
Joint swelling	0	2 (4%)	5 (10%)	4 (8%)
Myalgia	2 (4%)	1 (2%)	2 (4%)	5 (10%)
Pain in extremity	1 (2%)	2 (4%)	1 (2%)	4 (8%)
Nervous System	**11 (20.0%)**	**15 (26.8%)**	**12 (23.1%)**	**21 (40.4%)**
Areflexia	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Dysesthesia	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Hyperesthesia	1 (2%)	0	0	5 (10%)
Hypoesthesia	0	3 (5%)	2 (4%)	4 (8%)
Hyperreflexia	0	0	3 (6%)	2 (4%)
Hyporeflexia	0	4 (7%)	1 (2%)	1 (2%)
Pallanaesthesia	2 (4%)	2 (4%)	1 (2%)	4 (8%)
Paresthesia	3 (6%)	3 (5%)	0	3 (6%)

Safety Set (SAF)=all subjects who received any investigational product. Doses are mg/kg.

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Retrospective Collection of Joint Safety Data

- **Before Clinical Hold**
  - OA and Sciatica completed, other studies stopped due to poor enrollment
  - 2 TJR Cases During Studies
- **After Clinical Hold**
  - Investigators asked to contact patients and identify cases of TJR
    - 12 Additional Post-Study Cases / 10 Patients identified
    - Case information, X-Rays, Pathology obtained if possible

Overview of Joint-Related and Fracture Events

	OA Study		Non-OA Studies		
	REGN475 (N=160)	Placebo (N=55)	REGN475 (N=197)	Placebo (N=97)	Total
Total TJRs	10[a]	1	2	1	14
Fractures[a]	2[b]	0	0	0	2

[a]10 TJRs in 8 patients
[b]Patients with fractures did not have TJRs

Independent Adjudication of TJR Cases

- 3 Members: Rheumatologist, Bone Radiologist and Bone Pathologist
- Blinded independent review and then discussion at meeting
- Q1: Was case consistent with normal OA Progression?
- Q2: If not, was case consistent with ON, RPOA, or something else (explain)?

Adjudication Consensus Results

- 12 cases normal progression of OA
- No cases osteonecrosis
- 1 case Subchondral Fracture / Possible RPOA
- 1 case insufficient information

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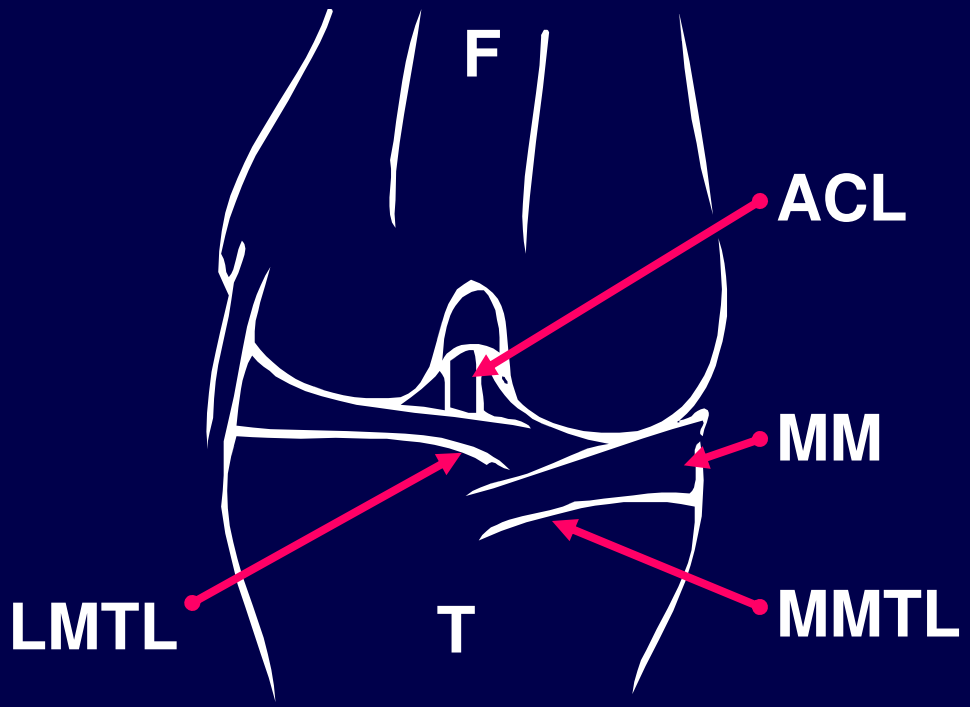
Non-clinical Study Caveats

- Small studies, 3 – 7 animals per group
- Some findings not yet reproduced
- Did not produce expected cartilage loss due to DMM surgery

Destabilization of the Medial Meniscus (DMM) Mouse Model of Osteoarthritis (OA) – Overview

- **Two DMM experiments conducted:**
  1. The effect of REGN475 monotherapy on OA-like joint
  2. The effect of REGN475 with or without a non-steroidal anti-inflammatory drug on OA-like joint



Destabilize the medial meniscus (MM) by surgical transection of the medial meniscotibial ligament (MMTL)

Glasson et al., 2007, Osteoarthritis and Cartilage

DMM Experiment #1: REGN475 Monotherapy for 16 Weeks Starting 1 Day after DMM Procedure

- **No significant effects of REGN475 on:**
  - Cartilage area or optical density
  - Bone volume, bone density, or bone mineral mass by microCT
  - Blood levels of the osteoclast marker TRAcP-5b
  - Vascular density
  - Sensory or sympathetic innervation

DMM Experiment #2: REGN475 Monotherapy vs. combination therapy with Indomethacin for 12 Weeks Starting 16 Weeks after DMM Procedure

- Pilot Study, additional analyses ongoing
- No significant effects of any drug treatment:
  - Vascular density
  - General bone pathology (GLP assessment by Veterinary Pathologist)
- No significant effects of REGN475 alone:
  - Cartilage area or optical density
- Suggestive but highly variable effects of REGN475 + indomethacin:
  - Decreased cartilage area and optical density (Safranin-O) in DMM group but not sham group
  - Elevated serum TRAcP-5b levels in REGN475 + Indomethacin-treated group regardless of surgery (DMM or sham)

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Proposed Regeneron / Sanofi Implementation: OA

- Prospectively explore dose and regimen that achieves clinically meaningful therapeutic index in OA patients with greatest need:
  - Superior to NSAIDs in poor NSAID responders
  - Superior to baseline therapy in NSAID intolerant patients
  - Superior to baseline therapy in patients awaiting TJR
  - Whether SC administration and shorter intervals improve safety by minimizing C_{max}
- Continue nonclinical studies to determine clinical relevance

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Sponsors' Proposed Path Forward

- Prospectively demonstrate a clinically significant benefit over existing options and an acceptable safety profile in patients with unmet need

Sponsors' Proposed Path Forward: Screening/Baseline evaluation

- Informed Consent
- Standardized X-Rays (shoulders*, hips, knees)
  - Central Reader
- Standardized pain questionnaire to evaluate all major joints

*OA studies only

Sponsors' Proposed Path Forward: Safety Exclusions

- Exclude chronic NSAID use
  - Limit to use for intercurrent events (fever, sprain, etc.) to match real-world setting
- Limit dose of anti-NGF treatment in OA
- Exclude patients with K-L 3/4 OA from studies in non-OA indications where higher doses of anti-NGF are used
- Exclude high risk patients (prior history of RPOA)

Sponsors' Proposed Path Forward: Ongoing Surveillance

- **All studies**
  - Standardized pain questionnaire at specified intervals to evaluate all major joints
  - End-of-study joint safety F/U for all patients including those who discontinue drug
- **OA studies**
  - Annual X-Rays hips and knees; Central Reader
  - Post-study (6 months) follow-up of joint safety (functional status and TJRs)
- **Surgical and 3-month post-operative outcomes in any patient who requires joint replacement**

Sponsors' Proposed Path Forward: Evaluation of Joint Specific Events

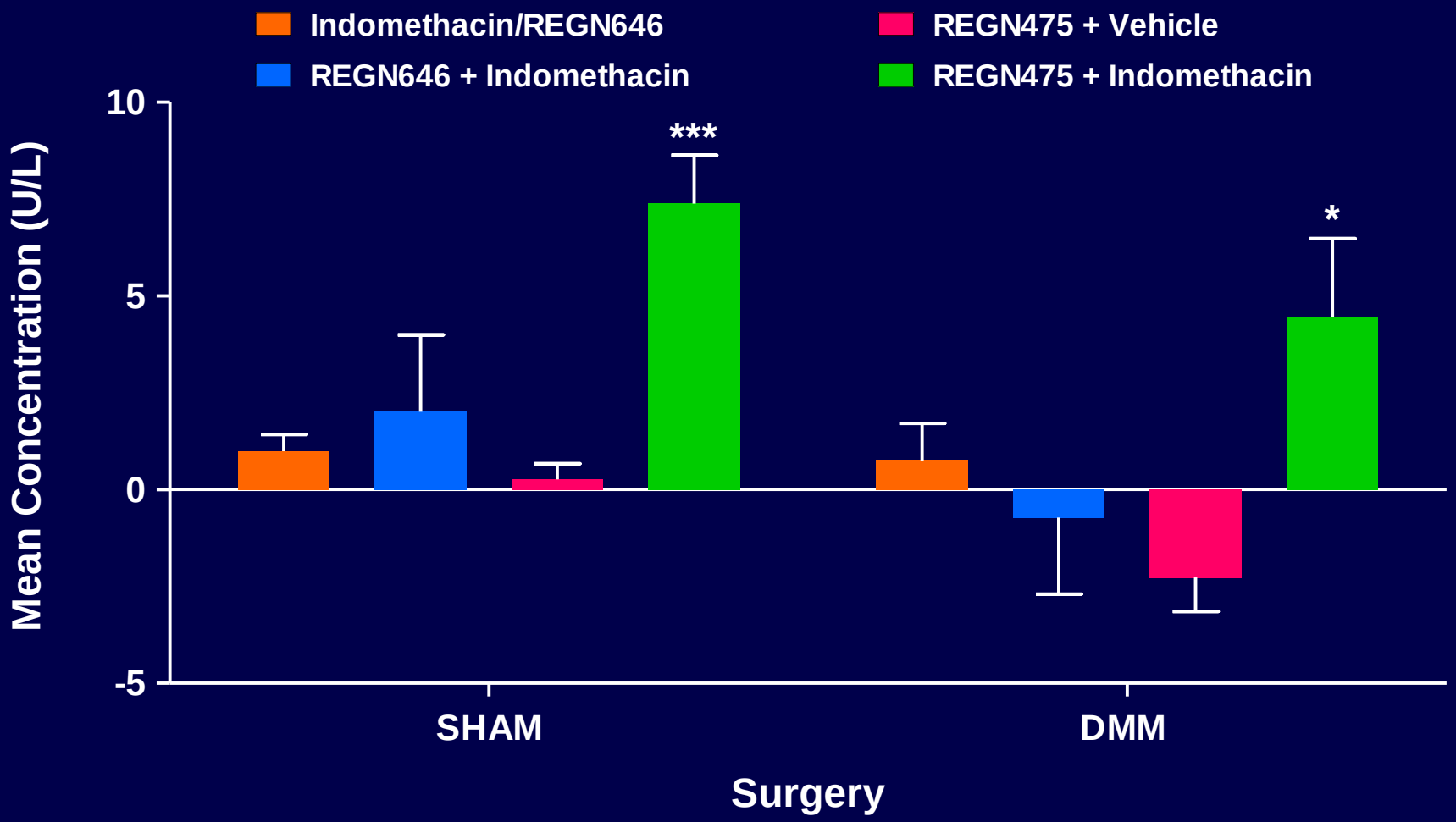
- Expanded collection of information
  - Clinical information including surgical reports
  - Original radiographs and other diagnostic images as appropriate
  - Pathology slides or tissue block (where possible)
- Information evaluated by centralized adjudication committee

Sponsors' Proposed Path Forward: Protect Patient Safety

- Thorough evaluation of new or worsening joint pain
- Discontinue therapy or increase surveillance in patients with new findings
- IDMC to monitor safety data

BACK-UPS

REGN475 + NSAID Combination Therapy Significantly Increases TRAcP-5b, a Serum Marker of Osteoclast Activity



*p<0.05
***p<0.001

Cartilage Evaluation Methodology

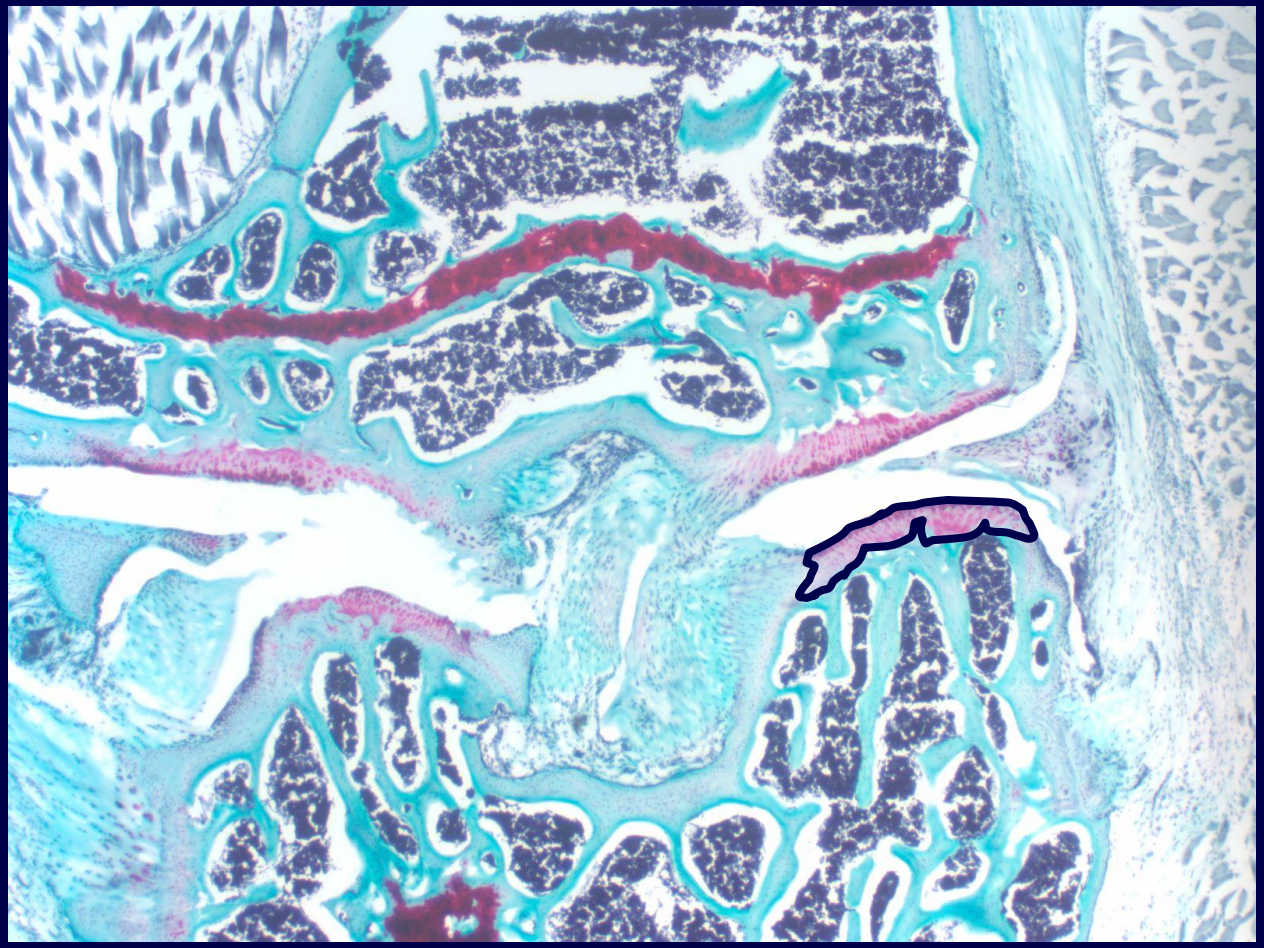


Image J Software Quantification: Area and Safranin O Optical Density